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Passive immunization for the public health control of communicable diseases

Current status in four high-income countries and where to next

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Abbreviations: GDP, Gross domestic product; HAV, Hepatitis A virus; IG, Immunoglobulin/Immune globulin; IgG, Immunoglobulin G; IU, International units; kg, kilograms; mg, milligrams; mL, millilitres; MMR, Measles, mumps, rubella; NZ, New Zealand; UK, United Kingdom; US, United States of America

The practice of passive immunization with human immune globulin (IG) for the control of communicable diseases (measles, rubella and hepatitis A) differs somewhat between Australia, the United States of America, the United Kingdom, and New Zealand despite the many similarities of these countries, including disease incidence rates and population immunity. No minimum effective dose of IG has been identified for protecting susceptible contacts of measles or hepatitis A. Recommended passive immunization practice for susceptible pregnant contacts of rubella is based on limited evidence in all countries. We suggest that gaps in the evidence base need to be addressed to appropriately inform the role of passive immunization in public health practice into the future.

Introduction

Passive immunization, the transfer of antibodies from donor to recipient,[1] is one key strategy for communicable disease control.[2] Passive immunization prevents disease via interaction between the administered antibodies and invading microorganisms.[3] The antibodies distribute throughout the recipient's extracellular spaces[4] and there may: neutralize invading virus particles by directly preventing their entry into cells;[4] block cell surface receptors, thus preventing viral entry into cells;[3] activate the complement cascade (another part of the immune system) resulting in destruction of the virus;[5] coat the virus to assist its engulfment (phagocytosis) by immune cells (a process known as opsonisation);[4] or facilitate destruction of infected cells (antibody dependent[5] or complement dependent cytotoxicity[6]).

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As early as the late 1800s, the short-term protection against infectious diseases afforded by passive immunization was being investigated, with convalescent human serum first being utilized for the prevention of measles in 1907.[7,8] Over subsequent decades, convalescent serum, either from individuals or from a small number of donors pooled together, was documented to prevent or ameliorate disease when administered to non-immune people within a short time of exposure.[8] During the 1930s, this practice of post exposure prophylaxis via passive immunization was widespread in the medical community.[8]

Passive immunization continued to be the mainstay of the public health management of hepatitis A and measles prior to the availability of vaccines.[1] However, rather than administering antibodies in the form of the serum of convalescents, human immune globulin (IG) came to be recognized as the blood product of choice.[1]

IG is a concentrated solution of plasma proteins, almost all of which are antibodies.[9] It is one of the blood products produced by the process of Cohn cold ethanol fractionation of the pooled plasma of at least 1000 blood donors.[10] The process uses ethanol at varying concentrations, levels of acidity, temperatures and ionic strengths to precipitate proteins of different molecular weights at different stages and collect these by filtration.[11]

Today, passive immunization with IG still plays an important part in the prevention of measles and hepatitis A among non-immune contacts in countries with low incidences of these diseases.[12-18] In some cases passive immunization is also recommended for non-immune pregnant contacts of rubella.[16,19-22]

However, public health management of these diseases is inconsistent between developed countries such as the United Kingdom (UK), the United States (US), Australia and New Zealand (NZ);[12-18,21-28] and the recommended management of non-immune pregnant women exposed to rubella is also inconsistent within Australia.[19,20,29] This narrative review of the literature briefly outlines these differences and then seeks to explore

Table 1. Current recommended passive immunization practices of four high-income countries

		Australia	United Kingdom	United States	New Zealand
Measles	Contacts for post exposure passive immunization	Up to 6 d after first exposure if: • >72 h since first contact with case • <9 mo old • pregnant • immunosuppressed[12]	Up to 6 d post exposure: • <9 mo old • pregnant • immunosuppressed **• Not recommended for others even if >72 h post exposure**[23]	Within 6 d of exposure if: • >72 h since exposure • ≤12 mo old • pregnant • immunocompromised • vaccine contraindicated[17,94,95]	Up to 6 d after exposure if: • >72 h since exposure • <15 mo old • pregnant • immunocompromised • vaccine contraindicated[16] (**Auckland district health board: Only if susceptible AND immunosuppressed/pregnant/<6 mo old. NOT others even if >72 h post exposure**)[28]
	IG* dosage	• 0.2 ml/kg • immunosuppressed: 0.5 ml/kg[12]	• Nil • immunosuppressed 0.6 ml/kg • infants 0.6 ml/kg • pregnant women 2250 mg (3 vials)[23]	• 0.25 ml/kg (max = 15 ml) • immunocompromised 0.5 ml/kg (max = 15 ml)[95]	• 0.6 ml/kg (max = 5 ml for healthy infants and 15 ml for others)[16]
Hepatitis A	Contacts for post exposure passive immunization	Within 2 weeks of last exposure to an infectious case: • <12 mo of age • immunosuppressed • chronic liver disease • vaccine is contraindicated[13]	Within 2 weeks of exposure to the index case: **• Not infants** • ≥50 y of age • chronic liver disease • chronic hepatitis B or C infection **Hepatitis A vaccine co-administered.**[15]	Within 2 weeks since exposure: • <12 mo of age • ≥41 y of age • immunocompromised • chronic liver disease • vaccine is contraindicated[27]	Within 2 weeks since exposure: • <12 mo of age • ≥41 y of age • immunocompromised • chronic liver disease[16]
	IG* dosage	<25 kg 0.5 mL 25–50 kg 1.0 mL >50 kg 2.0 mL[13]	<10 y 500 mg ≥ 0 y 750 mg (750 mg is approx. 5 mL)[24]	0.02 mL/kg[27]	0.02 mL/kg[16]

*IG – Immune globulin.

the possible reasons behind them to help inform future public health practice.

Current Passive Immunization Practices

Passive immunization practices vary between Australia, UK, US and NZ in respect of those contacts offered human IG, the dose of IG that is administered, or both (**Table 1**). In the case of rubella, until very recently, each country's national recommendations suggested only offering IG to exposed pregnant women for whom termination of pregnancy is not acceptable. The latest Australian Immunization Handbook, published this year, omits this requirement, but does not go so far as to recommend IG for all non-immune pregnant women.[30] The rationales for restricting IG to susceptible pregnant women refusing termination differ among the other countries. The UK Immunoglobulin Handbook suggests IG "*does not prevent infection in non-immune contacts but may reduce the likelihood of clinical symptoms, which may possibly reduce the risk to the foetus*";[22] the NZ Immunization Handbook states "*Although IG has been shown to reduce clinically apparent infection in the mother, there is no guarantee that foetal infection will be prevented*";[16] and the US Centers for Disease Control recommendations state "*Administration of IG after exposure to rubella will not prevent infection or viremia, but might modify or suppress symptoms and create an unwarranted sense of security.*"[17,21]

Possible Reasons for Differences in Current Passive Immunization Practice

Australia, UK, US and NZ are similar in a number of ways. They are all top 30 countries as listed by gross domestic product (GDP) per capita by the World Bank.[31] They are all grouped as 'high income' countries by the World Health Organization for burden of disease reporting.[32] Australia, UK, and NZ have similar spending on health, both as a percentage of GDP and per capita, according to Organisation for Economic Co-Operation and Development data, though the US spends roughly twice that of these other countries (**Table 2**).[33] While the populations differ in terms of ethnic groups and their proportions, the majority of each country's population is white.[34] Population health status, as measured by life expectancy at birth,[33] infant mortality[33] and rates of all cause disability adjusted life years[35] is similar (**Table 3**). The contribution of communicable and non-communicable diseases to each country's burden of disease is also similar.[35]

Table 1. Current recommended passive immunization practices of four high-income countries (continued)

		Australia	United Kingdom	United States	New Zealand
Rubella	Contacts for post exposure passive immunization	Immunization Handbook • 9th edition published 2008 - only *"if termination for confirmed rubella would be unacceptable under any circumstances"*[96] • 10th edition published 2013–above statement has been removed.[30] Queensland • refer non-immune exposed pregnant woman to obstetrician for "frank" discussion of the risks and possible benefits within 72 h of exposure[20] Victoria • consider immunoglobulin after exposure to rubella in early pregnancy as "*it may modify abnormalities in the baby*"[19] New South Wales • immunoglobulin has not been demonstrated to be of value post-exposure[29]	Only if termination for proved rubella infection is unacceptable to non-immune pregnant woman.[22]	Consider only if pregnant woman exposed to rubella will not consider termination under any circumstances. In these cases, administer immunoglobulin within 72 h of exposure.[21]	May be considered if termination of the pregnancy is not an option.[16]
	IG* dosage	20 mL[30]	750 mg (approximately 5 ml)[22]	20 mL in divided doses[21]	Recommended dose not given[16]

*IG – Immune globulin.

What then is contributing to differences in the practice of passive immunization for controlling communicable diseases? We examine each of the following possible reasons: disease-specific incidences; disease-specific population immunity; relevance of literature; evidence of the effectiveness of passive immunization; cost effectiveness; access to IG; and, levels of disease-specific antibodies in IG.

Incidence of Disease and Population Immunity

Australia, UK, US and NZ all have low incidences of these diseases (**Table 4**).[15,16,18,25,36,37] While some variation in rates exists across countries, and from year to year within countries, the differences do not appear to be large enough to impact significantly on the resources required for the public health management of these conditions in these affluent countries.

Each of these countries has a similar immunization schedule for these diseases, with the exception of the US that includes Hepatitis A vaccine on its childhood immunization schedule for all children.[16,30,38,39] Measles, mumps, rubella (MMR) vaccine coverage rates are also similarly high at around 90% of the target population.[37]

Hepatitis A population immunity is similar (**Table 4**), with low proportions of children and higher proportions of adults seropositive, but many adults still susceptible.[40] A study estimating overall prevalence in 2005 based on published figures reported very similar age-specific prevalence distributions across these countries.[41]

So too, measles and rubella immunity is similar, at over 90% of the surveyed populations (**Table 4**).[42-49] Age-specific seroprevalence distributions are also similar, with high proportions of all age groups immune subsequent to the second MMR scheduled dose, although lower proportions of adult males than females are immune to rubella when these comparisons are available.

Overall, differences in population immunity are unlikely to contribute to differing public health management recommendations for these diseases.

Table 2. Expenditure on health of four developed countries, 2009[33]

Health expenditure	Australia	United Kingdom	Untied States	New Zealand
Percentage of gross domestic product	9.1	9.8	17.7	10.0
Per capita (US$)	3670	3379	7990	2923

Table 3. Overall population health of four developed countries

Marker of Population Health	Australia	United Kingdom	United States	New Zealand
Life expectancy at birth (F/M) 2010[33]	84.0/79.5	82.6/78.6	81.1/76.2	82.8/79.1
Infant mortality (deaths per 1000 live births) 2009[33]	4.3	4.6	6.4	5.2
Age standardized DALYs* per 100 000 all causes 2004[35]	9894	11012	12844	10642
Age standardized DALYs* per 100 000 Infectious and parasitic diseases 2004[35]	155	187	330	144
Age standardized DALYs* per 100 000 non-communicable diseases 2004[35]	8222	9576	10481	8831

*DALYs – disability adjusted life years

Table 4. Comparison of four high-income countries on disease-specific possible reasons for differences in passive immunization practices

		Australia	United Kingdom	United States	New Zealand
Measles	Incidence[37]	$0.31/10^5$ (2010)	$0.71/10^5$ (2010)	$0.023/10^5$ (2009)	$0.98/10^5$ (2010)
	Immunization Schedule[37]	12 mths and 4 y	13 mths and 3–5 y	12–15 mths and 4–6 y	15 mths and 4 y
	Vaccine coverage[37]	88% 2 vaccines (2010)	87% 2 vaccines (2010)	90% 1 vaccine (2010)	91% 1 vaccine (2010)
	Serosurvey evidence of immunity	94% (2002)[42]	>90% adults (2000)[43]	96% aged 6–49 y (1999–2004)[44]	94% aged 6–44 y (2009)[45]
	Antibody level in IG	Unknown	23–39 IU/mL[14]	Standardized against reference lot[93]	14–16 IU/mL[28]
Hepatitis A	Incidence	$1.1/10^5$ (2006–7)[36]	$0.68/10^5$ in England and Wales (2009)[97,98]	$1.9/10^5$ (2004)[18]	$1.1/10^5$ (2010)[16]
	Immunization schedule	Indigenous children in high risk areas at 12–18 and 18–24 mths[30]	Not on Childhood Immunization schedule[25]	All children at 12 mths and 18–23 mths[99]	Not on Childhood Immunization schedule[16]
	Serosurvey evidence of immunity	41% (all ages) (1998)[100]	30.7% (all ages) in England and Wales (1996)[101]	34.9% (6+ yrs) (1999–2006)[102]	27.9% (adults 18+ yrs) (1996)[103]
	Antibody level in IG	≥100 IU/mL as per European Pharmacopeia (pers comm D. Maher, CSL)	60.3–86.8 IU/mL[15]	Unknown—varies by batch[18]	≥100 IU/mL as per European Pharmacopeia (pers comm D. Maher, CSL)
Rubella	Incidence	$0.23/10^5$ per yr (2006–07)[36]	$0.06/10^5$ (lab confirmed cases only) (2008)[104]	Approx $0.01/10^5$ (2009)[105]	$0.5/10^5$ (2011)[106]
	Immunization schedule and Vaccine coverage	As for measles	As for measles	As for measles	As for measles
	Serosurvey evidence of immunity	94% aged 19–49 y (1997–98)[46]	>90% aged >3 y (1994–1998)[49]	91% aged 6–49 y (1999–2004)[48]	92% aged 6–44 y (2009)[45]
	Antibody level in IG	Unknown	Unknown	Unknown	Unknown

Relevant Literature

Evidence of efficacy and effectiveness of passive immunization is generalisable globally. To apply evidence of safety, donor population prevalence of blood borne diseases may need to be taken into account. These countries all have low population prevalences of hepatitis B, hepatitis C and human immunodeficiency virus, and effective virus detection and neutralization steps in IG production.[9,50-54] To apply evidence of cost effectiveness, disease incidences, population immunity, and health system factors need to be taken into account. As discussed above, disease incidences and population immunity are similar. However, the health systems of these countries differ considerably, particularly in terms of financing and the roles of government.[55,56] This may impact on the generalisability of cost effectiveness evidence.

Evidence of Effectiveness

No systematic review evidence of the effectiveness of passive immunization for the prevention of measles currently exists. Zingher's presentation to the Pediatrics Section of the New York Academy of Medicine in 1924 cites a number of early studies.[8] More recently, Ramsay et al.[14] cite a number of observational studies and one controlled study as evidence of the effectiveness of post exposure IG for preventing measles. They report large variation in the estimates of effectiveness, and note the possible role of IG dose in this. Neither of these publications consider all current relevant studies (for example, Harper et al.[57] and Sheppeard et al.[58] have not been included).

No systematic review evidence of the effectiveness of passive immunization for the prevention of rubella currently exists. Further, the evidence on which public health practice is based is limited and somewhat contradictory. The Australian Immunization Handbook references the US guidelines for each of the statements about post exposure passive immunization for rubella.[30] These Australian guidelines state that post exposure passive immunization "*does not prevent infection in non-immune contacts*."[30] Whereas, the NZ guidelines state that "*IG has been shown to reduce clinically apparent infection in the mother*," but do not reference this statement.[16] The US guidelines provide two references at the end of the paragraph on post exposure passive immunization against rubella.[17] One is a primary controlled study on passive immunization under experimental conditions that indicated efficacy of high dose IG within 24 h of exposure, but limited efficacy at lower doses.[59] The other is a book chapter that does not include in-text citations.[60] It states that: "*Immune globulin may reduce clinical findings, but does not prevent viraemia*." There is no indication of the dose of IG, anti-rubella Immunoglobulin G (IgG) concentration, or timing of administration to which this statement is referring. The statement conflicts with the study by Schiff[59] (the other reference used in the US guidelines) that concluded viraemia was prevented with high-dose IG. Waagner's book chapter[60] goes on to indicate the author's personal preference for only using immunoglobulin for pregnant women presenting within 72 h of exposure for whom therapeutic abortion is not an option. The author reasons that asymptomatic maternal infection may occur, anti-rubella antibody titers in immune globulin vary, and infants have been born with congenital rubella syndrome despite post exposure passive immunization. The author does not consider the possibility of detecting asymptomatic infection in women post IG administration using serial serological testing, despite recommending exposed pregnant women undergo such testing immediately post exposure, and then at two to three and six weeks post exposure.

No primary research evidence has been published in the last three decades on the use of IG generally for preventing rubella in non-immune exposed pregnant women. Schiff and other literature from the 1970s and earlier draws varying conclusions, but may indicate a degree of efficacy.[1,59,61-67] The studies tended to be underpowered making firm conclusions difficult without meta-analysis. The difference between anti-rubella antibody titers in today's IG and these studies also requires consideration.

Two systematic reviews of passive immunization for the prevention of hepatitis A have been published. Liu et al.[68] included two randomized controlled trials examining post exposure prophylaxis. Mosley et al.[69] examined two different IG products from the same manufacturer, produced at different times, vs. placebo, finding one to be effective and the other not. The anti-hepatitis A virus (HAV) IgG content of the products was not identified. Victor et al.[70] compared IG and vaccine, finding both were equally efficacious for susceptible contacts aged two to 40 years. Again, the anti-HAV IgG content of the blood product used was not identified. However, the UK hepatitis A public health guidelines[15] identify the IG product used in the trial by Victor et al. contained 18.83 IU/mL of anti-HAV IgG. The two included trials in this review[68] were clearly unable to be combined in meta-analysis.

Bianco et al.[71] included two studies examining post exposure prophylaxis. These authors also included Mosley et al.'s study.[69] The second included study was a quasi-randomized multi-center controlled trial that reported post exposure prophylaxis with British IG to be effective.[72] Again, the anti-HAV IgG content of the blood product used was not identified. Bianco et al. combined these trials in meta-analysis to give an overall effectiveness estimate of 69%.[71]

The UK guidelines for the public health management of hepatitis A include a summary of the evidence base for post exposure prophylaxis with IG.[15] The guidelines cite a number of randomized studies not included in the above systematic reviews, and a number of non-randomized controlled trials and observational studies. Critique of the methods of these studies is not included. The guidelines point out the varying estimates of effectiveness of post exposure IG for the prevention of hepatitis A.

Evidence of Cost Effectiveness

The cost effectiveness of post exposure passive immunization for the prevention of measles and rubella has not been considered in the medical literature. Two studies report on the costs of health system responses to measles including passive immunization (one from a public health perspective and one from a health service perspective), but costs per case prevented were not given and could not be calculated from the published information.[73,74]

Evidence on the cost effectiveness of post exposure passive immunization for preventing hepatitis A is limited in general, and absent from UK, NZ or Australian settings. Providing IG to all visitors to a National Park in the US where drinking water had been contaminated by sewage was determined not to be cost beneficial on post-event analysis.[75] Pavia et al.[76] determined the attributable risk reduction of a mass campaign to passively immunize the residents in a religious community in the US during a hepatitis A outbreak to be 33.8/1000 over a seven-month period. The cost per case prevented can be calculated from their results as US$47.63. Gillis et al.[77] compared the cost effectiveness of the Israeli Defense Forces program of passive immunization against hepatitis A (including both pre and post exposure prophylaxis) with active hepatitis A vaccination. The cost per case prevented by passive immunization depended on the incidence of disease

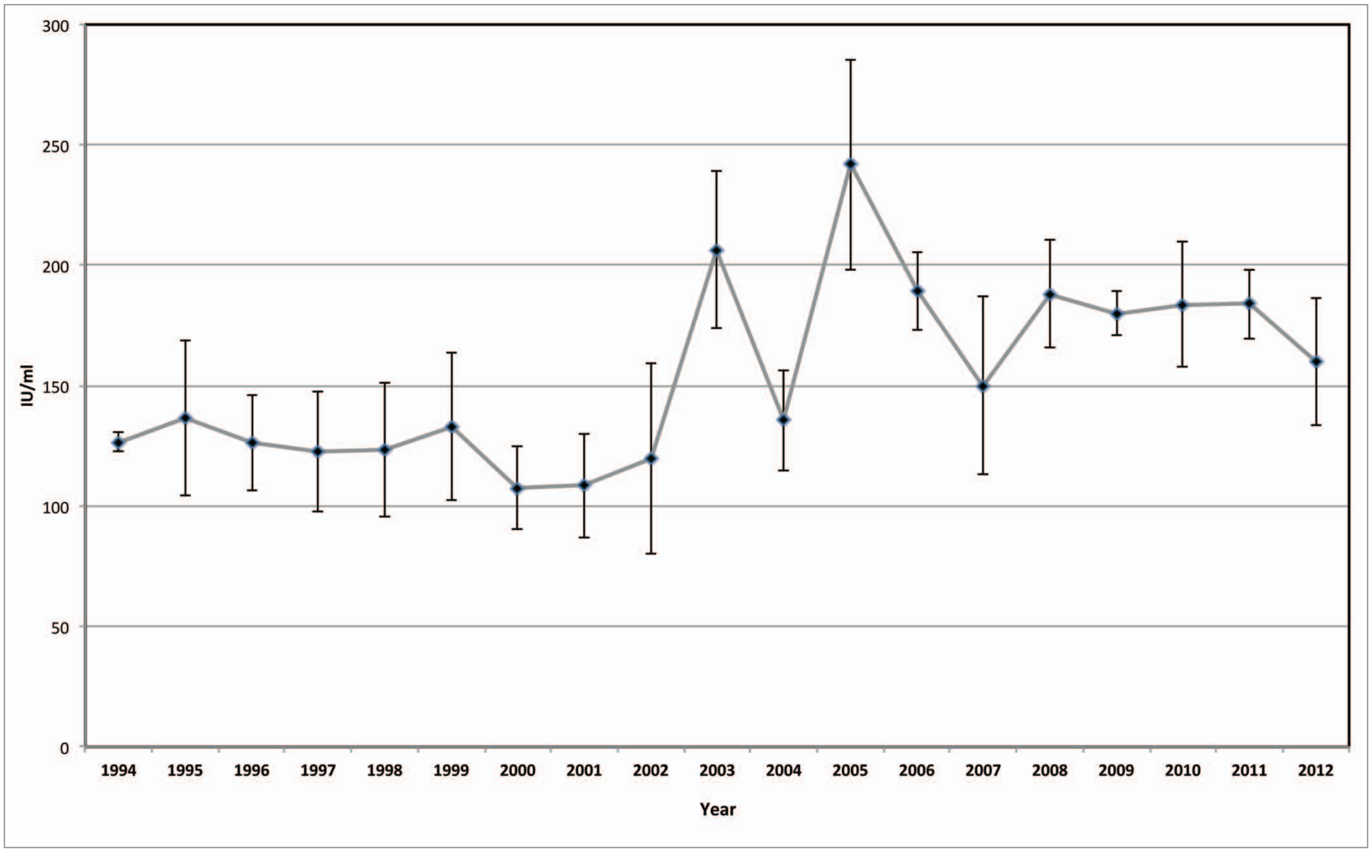

Figure 1. Measured anti-Hepatitis A virus IgG in Australian immune globulin produced by CSL Biotherapies 1994–2012, means and standard deviations (Courtesy of CSL Biotherapies, Australia).

assumed, the duration of service, and the state of living conditions and ranged from US$48.53 to US$810.78. A cost-benefit analysis of passive immunization of children and pregnant women in Israel in response to fecal contamination of a water supply did not support the practice.[78] The cost to prevent one child case was estimated at US$362.50, and the cost to prevent one case among pregnant women was estimated at US$11 514. Particularly notable in this study was the assumptions made about the attack rates in the subject populations and the accompanying lack of sensitivity analysis.

Access to IG

Available evidence suggests that access to IG is similar in the USA, UK, NZ and Australia. Each of these countries has one or more national blood collection programs[79-83] and collection rates are all at least 30 donations per 1000 population,[84] although, the UK imports plasma for the production of IG because of the theoretical risk of bovine spongiform encephalitis transmission.[85,86] Two different practice manuals in the UK suggest IG is readily available from pharmacies and through the Health Protection Agency.[23,85] A June 2012 presentation to the Advisory Committee on Immunization Practices Meeting suggested that intramuscular IG is readily available in the US, although distribution is sometimes an issue.[87] New Zealand reports self-sufficiency in terms of blood and plasma products.[86,88] Australia too, is able to meet demands for IG locally.[86,89]

Disease-Specific Antibody Titers in IG

The Australian product information for IG indicates the product contains 160 mg/mL of human plasma proteins, mainly IgG. However, the disease-specific levels of IgG are not listed.[9] CSL Biotherapies Australia Ltd. (personal communication: Darryl Maher, Senior Director, Medical and Research) confirmed that IG is manufactured to the European Pharmacopeia standard for hepatitis A antibodies of ≥ 100 IU/mL.[90] Blood donors with high levels of hepatitis A antibodies are specifically selected for the IG pool. Each batch of IG is tested to ensure the concentration of anti-hepatitis A antibodies is at least 100 IU/mL (**Fig. 1**). Measles and rubella antibody levels are not routinely measured in the product (personal communication: Darryl Maher, Senior Director, Medical and Research, CSL Biotherapies Australia Ltd).

CSL Biotherapies Australia Ltd. also manufactures IG for NZ, using NZ plasma donations. The manufacturing process is identical to that of Australian Biotherapies IG and the European Pharmacopeia standard for hepatitis A antibodies is applied (personal communication: Darryl Maher, Senior Director, Medical and Research, CSL Biotherapies Australia Ltd).

The IG product used for hepatitis A post-exposure prophylaxis in the UK was determined to contain anti-hepatitis A antibody levels between 60.3 and 86.8 IU/mL in 2008.[15] The UK report altering the public health guidelines for the management of hepatitis A in response to this.[15]

The anti-hepatitis A antibody levels in US IG has been reported to vary by batch, but no range was given.[18] Changes to US hepatitis A recommendations were made in 2007 in light of new evidence about post-exposure vaccination, but not hepatitis A antibody levels in IG.[18,27]

The UK and NZ measured measles-specific antibody levels in their IG products in 2009, finding concentrations of 23 to 39 IU/mL and 14 to 16 IU/mL respectively.[14,28] The UK measured antibody levels by plaque neutralization, while the methodology for measuring the NZ antibody levels is not identified. Different testing methods may account for some of the difference between countries.[91] Both the UK and at least one NZ region report adjusting the public health management of measles in response to this.[14,28] They base their adjusted dosage recommendations on the study by Endo et al. that identified anti-measles antibody levels between 16 and 45 IU/mL as measured by haemagglutination inhibition in commercially available preparations of IG in Japan in 1999 and 2000.[92] The US manufactures IG standardized to a reference lot for measles antibodies.[93]

No published levels of anti-rubella antibodies in IG were identified.

Conclusions

Passive immunization plays a defined, but important role in the public health control of communicable diseases in the developed world. There are current differences in practice with respect to passive immunization for measles, hepatitis A and rubella contacts between the high-income countries considered here. Particularly, passive immunization seems to play a lesser role in the public health management of hepatitis A and measles in the UK compared with the US, Australia and NZ, with fewer groups of contacts recommended for this intervention. Further, recommended doses of IG for post exposure prophylaxis vary considerably across the four countries.

Disease incidence, population immunity levels and access to IG are unlikely to account for the differences. Given the sparse evidence of cost effectiveness of this intervention with respect to hepatitis A, the lack of evidence of cost effectiveness with respect to measles and rubella, and accepting the generalizability of the evidence of effectiveness and safety, it is also unlikely that these countries are applying different literature evidence when forming their guidelines.

However, there are gaps in the evidence base on the effectiveness of post exposure IG for preventing these diseases. There is no systematic review evidence of the effectiveness of passive immunization for preventing measles or rubella. Particularly, the current recommendations about passive immunization and rubella control seem to hinge mainly on one reference that itself does not seem to be grounded solidly in the available evidence. While systematic reviews of the evidence for preventing hepatitis A exist, they have not been able to explore the minimum effective dose of IG. Differing administered doses may somewhat account for varying estimates of effectiveness.

Further, the disease-specific antibody content of IG varies considerably across these countries and over time. Decreasing levels of some disease-specific antibodies in IG has been reported to be the reason behind recent changes to practice in the UK and NZ. Anti-measles IgG and anti-rubella IgG levels in Australian IG are currently unknown.

These uncertainties could well account for the differences in practice across these countries, combined with the practical implications of differences in health system structures. Given the public health resources invested in the control of these diseases (upwards of US$100 000 for one reported case of measles)[73] we suggest that the magnitude of the role that passive immunization plays in these efforts should be informed by a strong evidence-base.

We suggest that systematic review evidence on the effectiveness of passive immunization for the post exposure prophylaxis of measles and rubella is required, as well as a broader review of the evidence on the effectiveness of passive immunization for post exposure prophylaxis of hepatitis A to attempt to address the question of minimum effective dosage. Relevant disease-specific antibody titers in IG should be measured periodically, say every 5–10 years, when not otherwise a part of routine manufacturing. And ultimately, local cost effectiveness studies would contribute to appropriately considered recommendations for passive immunization in public health practice into the future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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